American Journal of Hematology 61:98–102 (1999)

Comparative Response to Splenectomy in Coombs-Positive Autoimmune Hemolytic Anemia With or Without Associated Disease

Gorgun Akpek,* David McAneny,[2] and Lewis Weintraub[1]

[1]Section of Hematology/Oncology, Boston University School of Medicine, Boston, Massachusetts
[2]Surgical Oncology, Boston University School of Medicine, Boston, Massachusetts

We reviewed our experience in 30 patients with direct Coombs-positive (DAT+) autoimmune hemolytic anemia (AHA) who underwent splenectomy. Twelve patients had idiopathic "warm" AHA (group I) and 18 had AHA associated with systemic diseases (group II). Complete response to splenectomy was defined as having normal hemoglobin and reticulocyte count lasting for at least 6 months without subsequent medical therapy. Subnormal but greater than 50% improvement in these parameters with or without medical therapy was considered to be a partial response. Median age was 64 (23–81) in group I and 68 (23–76) in group II. Median follow-up duration was 18 and 10.9 months, respectively. Nine of 11 (82%) evaluable patients with idiopathic AHA and 3 of 16 (19%) patients with associated disease achieved a complete response. Partial response was obtained in 2 (18%) and 6 (37%) patients in groups I and II, respectively. Both complete-response and overall-response rates were statistically different between two groups (P = 0.001 and 0.02). Postoperative courses of group I patients were uneventful except for one who developed a subphrenic abscess. Five patients in group II developed bacterial infections, which were mostly pneumonias. Our findings indicate that splenectomy is an effective treatment approach with low morbidity and mortality in patients with refractory idiopathic AHA. It should, however, be considered cautiously in AHA patients with underlying systemic diseases because of its decreased efficacy and increased surgical morbidity in this subgroup. Am. J. Hematol. 61:98–102, 1999.

Key words: hemolytic anemia, splenectomy

INTRODUCTION

Acquired "warm" autoimmune hemolytic anemia (AHA) may present de novo (idiopathic) or be associated with other diseases such as systemic lupus erythematosus, lymphoma, or chronic lymphocytic leukemia. The diagnosis is established by demonstrating the presence of IgG or IgG and complement on the red-cell membrane utilizing the direct Coombs test. The attachment of antibody to the red-cell membrane results in increased splenic sequestration and destruction by splenic macrophages which express specific receptors for the Fc fragment of the IgG molecule [1,2]. Therefore, splenectomy has been advocated as a treatment modality in cases who are refractory to steroid therapy or those who relapse shortly after an initial response to the drug.

Previous reports suggest that two thirds of patients with idiopathic AHA will have a partial or complete remission following splenectomy [3]. Some of these patients require further glucocorticoid therapy commonly at lower dosage than they required before splenectomy to maintain acceptable hemoglobin levels [2]. Although the role of splenectomy in "warm" AHAs is well established, the outcome after splenectomy in AHA patients with underlying systemic diseases as compared to the idiopathic variety has not been particularly investigated. In the present study, we retrospectively evaluated the response to splenectomy in two groups of patients with Coombs-positive autoimmune hemolytic anemia.

Correspondence to: Gorgun Akpek, M.D., Section of Hematologic Malignancies, Bone Marrow Transplant Program, Johns Hopkins Oncology Center, 600 North Wolfe Street, Baltimore, MD 21287-8985.

Received for publication 16 July 1998; Accepted 3 February 1999

PATIENTS AND METHODS

Medical records of 30 consecutive patients with Coombs-positive AHA who underwent splenectomy at Boston University Medical Center between 1978–1997 were reviewed. Diagnosis of AHA was made based upon the presence of anemia associated with positive direct anti-globulin (Coombs) test by using IgG and complement as anti-sera, along with other hemolytic parameters such as increased reticulocyte count, lactate dehydrogenase (LDH), indirect bilirubin and decreased haptoglobin. The cases with drug-induced immune hemolytic anemia were not included in analysis. AHA with no associated disease was termed as idiopathic hemolytic anemia (group I). AHA patients associated with underlying systemic disorders were put in group II. Group II patients who were receiving specific treatment for the underlying condition were classified as having "active" disease. Those patients who had an associated systemic disease but who not were treated were considered to have "inactive" disease.

Hematologic response to splenectomy was evaluated at 2, 6, and 12 months after the operation. The patients who did not completely respond to splenectomy were given additional medical therapies in an attempt to maintain a hemoglobin level in an acceptable range. Response was defined as *complete response:* normal hemoglobin with no additional therapy lasting for at least 6 months after splenectomy, *partial response:* at least 50% improvement in hemoglobin level with or without additional treatment, *no response:* no improvement or marginal improvement (<50%) in hemoglobin with requirement of additional continuous medical therapy.

Postoperative complications that occurred between splenectomy and discharge from the hospital were defined as acute complications. Other subsequent events during the follow-up after discharge were considered as late clinical events.

Statistics

Descriptive analysis was performed to present the data. Comparisons were made by using the Fisher's Exact Test (2-tail). A P value of less than 0.05 was regarded as significant.

RESULTS

Patient Characteristics

The outcome of 30 patients with AHA who underwent splenectomy was analyzed. Of these, 12 had idiopathic AHA (group I), and 18 patients had AHA associated with underlying systemic diseases (group II), which included chronic lymphocytic leukemia (n = 9), non-Hodgkin's lymphoma (n = 4), systemic lupus erythematosus (n = 3), mixed collagen vascular disease (n = 1), and myelofibrosis (n = 1). Median age was 64 (23–81) and 68 (23–76) in group I and II, respectively. Sex distribution was also similar in two groups. Patient characteristics are summarized in Table I. Prior to onset of AHA, 11 of 18 patients (61%) of group II had "active" systemic disease requiring specific therapy. Four patients (33%) in group I and 10 patients in group II (55%) required regular red-cell transfusions at variable intervals in addition to medical therapy in an attempt to maintain an adequate hemoglobin level before splenectomy. Median time to splenectomy was 8.8 months (range, 0.2 to 49) and 3.2 months (range, 0.3 to 104) for group I and II patients, respectively. Two patients in each group underwent splenectomy as an initial treatment approach for the AHA because of the severity of anemia and thrombocytopenia in a patient with Evan's syndrome, medical contraindication to use of steroid in another patient, and both diagnosis of suspected underlying lymphoproliferative disorder and treatment of AHA in two other patients.

TABLE I. Patient Characteristics

Patients characteristics	Idiopathic AHA (n = 12)	AHA with associated disease (n = 18)
Median age (range)	64 (23–81)	68 (23–76)
Sex	5M/7F	10M/8F
Associated thrombocytopenia	2 patients	7 patients
Coombs data		
Direct antiglobin test (Ig G+)	11	18
Complement (+) only	1	—
Free antibody in the serum	2	3
Treatment prior to splenectomy		
Steroid	10	14
Immunoglobulin	5	4
Danazol	3	1
Azathioprine	1	0
Chemotherapy	0	7
None	2	2
Transfusion dependent	4	10
Time to splenectomy (months, range)	8.8 (0.2–49)	3.2 (0.3–104)

Outcome

One patient in group I and two patients in group II were not evaluable for response because of death due to sepsis in postoperative period. All patients with idiopathic AHA demonstrated a response to splenectomy: 9 of 11 (82%) CR and 2 of 11 (18%) a PR. Overall response rate in the second group was 56% with only 3 of 16 (19%) demonstrating CR. The difference with respect to overall response and complete response between the two groups was statistically significant ($P = 0.02$ and $P = 0.001$, respectively). All partial responders (37%) in group II had to remain on or subsequently be treated with medical therapies starting in a median of 1 month (0–165 days) after the splenectomy. The amount of the medications was generally lower in 5 of 9 responders than that

TABLE II. Clinical Response to Splenectomy

Response	Idiopathic AHA (n = 11)	AHA with associated disease (n = 16)
Complete response	9 (82%)	3 (19%)
Partial response	2 (18%)	6 (37%)
No response	None	7 (44%)
Median follow-up (months)	18 (2–107.5)	10.9 (2–188)

was required before splenectomy. Among these, one patient went into a durable complete remission with the reinstitution of steroid and IVIG therapy, another patient had a major decrease in steroid requirement, another remained stable with regular dose of steroid, one patient responded to the same regimen that was given before the splenectomy, and the other patient remained stable with a smaller dose of steroid. Response data is summarized in Table II. A total of 9 patients in group II were receiving chemotherapy and/or immunosuppressive therapy for associated disease before splenectomy. There was no difference in response rates based on the presence or absence of active systemic disease in this group (Table III). As can be seen in Figure 1, the normalization of hemoglobin in patients with idiopathic AHA occurred a median of 2 months after splenectomy. The median hemoglobin level of group II patients remained under 10 g/dl during the follow-up period. Of 2 partial responders in group I, one 23 year-old male patient who had Evan's syndrome underwent splenectomy upfront because of the severity of his clinical presentation. This patient had to receive an immunosuppressive therapy following splenectomy, which resulted in complete hematologic remission. The other patient in this group, a 70 year-old male, maintained his hemoglobin levels around 11 g/dl without requiring additional therapy or transfusion until 510 days after splenectomy, when his autoimmune process flared up requiring steroid and IV immunoglobulin, which were able to control his hemolysis.

Mortality and Morbidity after Splenectomy

Three postoperative deaths occurred with one in group I and 2 in group II. The patient in group I underwent splenectomy during emergency surgery for a perforated ulcer while receiving steroid therapy. This patient succumbed to Gram-negative sepsis and adult respiratory distress syndrome (ARDS), which resulted in death on post-op day 28. This fatal complication was most likely due to ulcer perforation rather than splenectomy per se. One patient in group II had advanced non-Hodgkin's lymphoma and died on post-op day 4 secondary to Gram-negative sepsis. A diaphragm tear was also noted in this case. The second patient in this group had chronic lymphocytic leukemia (CLL) and developed a subphrenic abscess, aspergillus pneumonia, and enterococcal sepsis associated with exacerbation of hemolysis and a portal vein thrombosis. This patient died on day 30 after the surgery.

TABLE III. Relationship Between the Status of Underlying Disease and Response to Splenectomy in Group II Patients (n = 16)

	Response to splenectomy			
Associated diseases	CR	PR	Overall response	NR
CLL				
Active disease (n = 4)	—	2	2	2
Inactive disease (n = 4)	—	2	2	2
NHL				
Active disease (n = 3)	2	1	3	—
SLE				
Active disease (n = 1)	—	1	1	—
Inactive disease (n = 2)	1	1	2	—
Mixed collagen VD				
Inactive disease (n = 1)	—	—	0	1
Myelofibrosis				
Active disease (n = 1)	—	—	0	1
Overall				
Active disease (n = 9)	2	4	6*	3
Inactive disease (n = 7)	1	3	4*	3

*$P > 0.05$

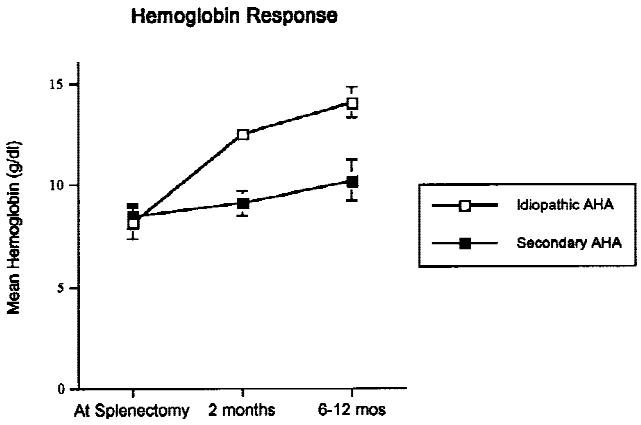

Fig. 1. Hemoglobin levels before and after splenectomy in patients with idiopathic AHA (open square) and those with systemic disease associated AHA (black square). Data are means with one standard error.

There was only one patient in group I who developed a subphrenic abscess as a nonfatal postoperative complication. The major nonfatal complications in group II patients included moderate intraoperative bleeding (n = 1), severe atelectasis (n = 1), wound dehiscence (n = 1), subphrenic abscess (n = 1), legionella pneumonia (n = 1), and acute arterial emboli requiring femora-popliteal bypass (n = 1).

Late Clinical Events after Splenectomy

Five patients in group I were noted to have thrombocytosis (>500.000/mm^3) and 2 had platelet counts of >1

million with no associated thrombotic events. A patient with Evan's syndrome had a pulmonary embolus shortly after being discharged from the hospital. This patient had a normal platelet count at the time of the event. Another patient who was receiving high-dose steroid before splenectomy developed aspergillus pneumonia during the early follow-up period. Bacterial pneumonia was seen in the other patient in this group. Late clinical events in group II patients included thrombocytosis (n = 2), left subphrenic abscess (n = 1), pneumocystis carinii pneumonia (n = 1), recurrent bacterial pneumonia (n = 1), recurrent bacteremia (n = 2), and pulmonary emboli (n = 1).

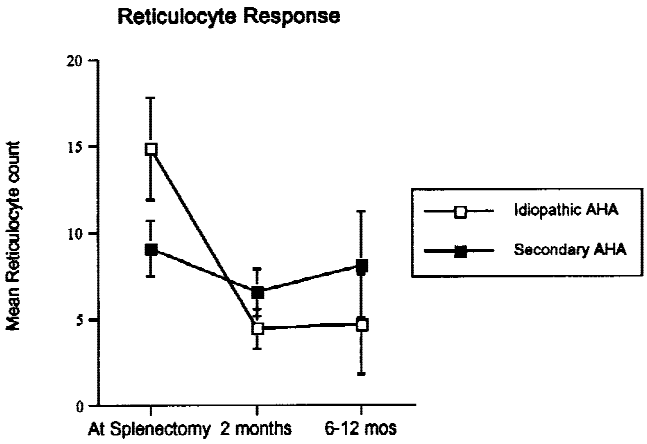

Fig. 2. Reticulocyte counts before and after splenectomy in patients with idiopathic AHA(open square) and those with systemic disease associated AHA (black square). Data are means with one standard error.

DISCUSSION

The initial management of AHA is a trial of corticosteroids, which can cause dramatic cessation or marked slowing of hemolysis in about two thirds of patients with AHA by several mechanisms. Steroid appears to decrease red-cell destruction by down-regulating the membrane Fc receptor sites for IgG on macrophages [4,5]. However, sustained remission after complete steroid withdrawal occurs in less than 20% of patients [5]. Several other therapeutic modalities including immunosuppressive drugs such as cyclophosphamide and azathioprine [7], danazol [8], high-dose intravenous γ globulin [9], and plasma exchange [10] have all been used to abort the hemolysis with limited, if any, long-term success. Therefore, substantial number of patients becomes a candidate for splenectomy during their course of disease to remove the primary site of red-cell trapping and destruction.

In a retrospective summary of several previously published series, improvement after splenectomy was observed in 60% of 316 cases [1]. The investigators from Germany recently reported the results of splenectomy in various hematological conditions, which were comparable to the literature with response rates of 60% and 78% in patients with AHA and thrombocytopenia, respectively [11]. These studies, however, failed to compare the results in idiopathic cases versus those with associated diseases. The data about the outcome after splenectomy in this subgroup of patients is very limited. Coon and et al. analyzed 52 patients with AHA who underwent splenectomy. However, only four of all the patients had an underlying disease [15]. The same investigator subsequently reported the outcome of seven patients with SLE who underwent splenectomy for hemolytic anemias [16]. In another retrospective analysis, splenectomy was also evaluated in 16 patients with systemic lupus erythematosus, Of those, thirteen patients had immune thrombocytopenic purpura and only 3 had AHA [17]. Similarly, Mestanza-Peralta et al. examined the outcome of splenectomy in 20 patients with immune thrombocytopenic purpura (ITP) including 14 patients with systemic lupus erythematosus (SLE) (36% with hemolytic anemia) [18].

Our experience with idiopathic AHA suggests a definite beneficial role of splenectomy in this group. In contrast, in those with associated disease, only half of the patients responded to splenectomy with three CRs. Furthermore, all partial responders in the latter group remained or subsequently were placed on additional medical treatment for hemolytic anemia.

Two of three complete responders in group II had non-Hodgkin's lymphoma and they received six cycles of cyclophosphamide, vincristine, and steroids chemotherapy for their underlying disease after the splenectomy. One could argue that the combination chemotherapy might have had an impact on maintaining a hematologic response in these two patients. Interestingly, no statistically significant difference was observed between group II patients with and without active systemic condition before splenectomy, suggesting that failure to respond probably be not related to the presence of disease activity.

As seen in Figure 2, the persistence of hemolysis in some patients seems to be the major cause of failure to splenectomy in group II. This could be partly related to persisting high levels of autoantibody, favoring red-blood-cell destruction in the liver by hepatic Kupffer cells [13,14]. Group II patients also had significantly lower presplenectomy reticulocyte counts compared to group I, suggesting that underlying lymphoproliferative disorders and/or previous chemotherapy may have impaired the bone marrow's response to hemolysis, thus affecting the outcome after splenectomy.

According to our data reported here, splenectomy is a very effective and safe treatment method for patients with idiopathic hemolytic anemia who are refractory to medical therapy. However, the same conclusion can not

easily be drawn for the second group. The major benefit of splenectomy in this second group seems to be an improvement in response to medical therapy after surgery. Five of 12 (41%) patients who were refractory to medical therapy maintained an adequate hemoglobin level with similar medical management after splenectomy.

We observed that postoperative morbidity in AHA was considerable in group II patients. This may be a manifestation of their underlying disease. The only mortality in the idiopathic group was due to Gram-negative sepsis and death, possibly because of emergent surgery performed for a perforated duodenal ulcer. The outcome could have been different if this patient had undergone splenectomy without this complication.

We have seen four cases with the development of a thrombosis during the follow-up after splenectomy (two pulmonary emboli, one portal vein thrombosis, and one acute arterial emboli). As after splenectomy for other reasons, evidence of thromboembolism is frequent at autopsy series. Portal venous thrombosis has been reported in 4 of 350 cases that underwent splenectomy for various hematologic disease. Three of these four patients had AHA [19].

Given the possibility of increased morbidity and mortality in some AHA patients undergoing splenectomy under general anesthesia, alternative approaches might be considered to remove the spleen or to decrease its function in sequestration. In a recent retrospective study, laparascopic splenectomy was reported to be an effective and safe technique that may be associated with a decreased incidence of postoperative complications [20]. Several other studies, however, emphasized the need of patient selection and careful search for accessory spleen to prevent the recurrence which is the main limitation of this approach [21].

Splenic irradiation, high-dose immunoglobulin and chemotherapy-induce immunosupression may also be considered on an individual basis in patients with associated lymphoproliferative disorders [22,23].

In conclusion, our findings indicate that splenectomy is quite effective and a relatively safe treatment approach in patients with idiopathic AHA who become refractory to medical therapy. The distinction between idiopathic AHA and AHA with associated systemic disease has not been previously demonstrated in terms of efficacy of splenectomy and postoperative complications. Based on the data presented above, the recommendation of splenectomy does not seem to be warranted for all AHA patients. Although there may be still some value of splenectomy in those with underlying systemic conditions, it should be considered cautiously for the management of Coombs-positive AHA in this group of patients because of relative lack of efficacy and increased surgical morbidity.

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